REMARKS

Claims 20-35 were pending in the application. Claims 36-38, withdrawn from consideration by the Examiner, have been cancelled without prejudice. Claims 20-35 stand rejected. Pending claims 20, 28, 30, 32, 33 and 35 have been amended. Claims 21-27, 29, 31 and 34 were cancelled without prejudice to presentation in future unrelated applications. New claims 39-42 have been added.

Support for the amendments to claims 20, 28, 30, 32, 33 and 35 and for new claims 39-42 can be found, for example, in paragraphs [0007], [0009], [0017], [0019], [0021], [0024], [0037], [0052], [0130], [0134], [0206], the originally filed claims, and Table 108 of the application as originally filed. Paragraph numbering is as set forth in U.S. published patent application 20070037145.

No new matter has been added.

Upon entry of this amendment, claims 20, 28, 30, 32, 33, 35 and 39-42 will be pending.

Rejections under 35 U. S. C. § 112, second paragraph

Claim 35 was rejected under 35 U. S. C. § 112, second paragraph, as allegedly indefinite due to the phrase "complement thereof". The Office asserts that "the term 'complement' includes polynucleotides that are not complementary to the reference sequence, [sic] where the 'complement' is complementary as either end of the sequence but not in the middle of the sequence, the scope of the claimed polynucleotides is indefinite." Although Applicants respectfully disagree and assert that one of skill in the art would readily understand the metes and bounds of claim 35, Applicants have amended claim 35 as suggested by the Office to read "or a <u>full</u> complement thereof."

In view of the foregoing Applicants respectfully request the reconsideration and withdrawal of the rejection under 35 U. S. C. § 112, second paragraph

Rejections under 35 U. S. C. § 112, first paragraph (written description)

Claims 21 and 24 were rejected under 35 U. S. C. § 112, first paragraph, for an alleged lack of written description support. The Office asserted that "there is no support in the specification for the use of measurement of differential expression of PPP3CC for the purpose of detecting a propensity towards cancer." Applicants do not agree.

Applicants respectfully point out that adequate written description support exists in the application as originally filed for detecting a propensity towards cancer by measuring differential expression of PPP3CC (see, for example, originally filed claim 18 discussing diagnosing a propensity to carcinoma; paragraphs [0017] and [0206] discussing diagnosing carcinomas, especially breast cancers, by assessing sequence and/or expression levels of CA genes). Notwithstanding the foregoing and solely in an attempt to further the prosecution of the present application to allowance, Applicants have cancelled claims 21 and 24 without prejudice, thereby rendering the rejection moot.

Rejections under 35 U. S. C. § 112, first paragraph (enablement)

Claims 20-35 were rejected under 35 U. S. C. § 112, first paragraph, for an alleged lack of enablement. The Office alleged that "the specification, ***while being enabling for methods of diagnosis of colon cancer comprising the differential detection of PPP3CC levels***, does not reasonably provide enablement for methods for diagnosing any and all cancers or for the detection of a propensity towards cancer ..." (Office Action, page 4; emphasis added). Applicants respectfully disagree.

Preliminarily, Applicants note claims 21-37, 29 and 31 have been cancelled without prejudice. As discussed, claims 20, 28, 30, 32, 33 and 35 have been amended.

Applicants respectfully submit that no undue experimentation would be required for a person of skill in the art to practice the presently claimed methods. This is particularly true given the level of skill in the art, the state of the art, and the teachings of Applicants' specification. First, the level of skill in the art can be characterized as being quite high. Clearly, those of skill in the art would have been quite capable of measuring levels of PPP3CC expression products without undue experimentation. The specification and the state of the art as of the priority date

of the present specification are replete with guidance as to how to isolate and detect PPP3CC mRNA and protein in both cell and tissue samples.

The Office summarizes that practicing the claimed methods would require undue experimentation to determine if "the method would function as broadly claimed." The pending claims are not broadly drawn to *every* cancer, *any* change in expression level, or using *any* control. The claims, as amended, are directed to specific cancers: colon cancer, carcinoma, lymphoma, prostate cancer, stomach cancer and breast cancer. The claims recite a specified degree of increased expression as indicative of these specific cancers. The claims specify controls comprising non-cancerous tissues. Any experimentation necessary to practice the claims as amended would clearly be routine.

Applicants respectfully redirect the Examiner to *In re Wands*, in which the court stated that "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (citing *In re Jackson*, 217 USPQ 804, 817 (Bd. App. 1982)). Thus, given the high level of skill in the art, the guidance provided by Applicant's specification, and the reasonable amount of experimentation involved, no undue experimentation would have been required for a person of ordinary skill to carry out the presently claimed methods. As such, the claims are fully enabled.

Although the Office acknowledged that "Lakshmikuttyamma [Lakshmikuttyamma et al., J. Cell Biochem., 95:731-739, 2005] demonstrates that ***increased levels*** and ***increased activity*** of calcineurin is found in deeply invading colon cancer cells, and that a moderate amount relative to non-cancerous tissues is found in colon polyps" ... and "concludes that calcineurin activity and amounts are related to development of colon carcinoma", paradoxically the Office alleges that "one cannot extrapolate from the data in Lakshmikuttyamma to a method where the diagnosis is based on observations of mRNA levels." The Office further asserts that "it would not be reasonable to extrapolate the data of Lakshmikuttyamma to a method for the diagnosis of any and all cancers." Additionally, the Office alleges that further research would be required to establish "that calcineurin protein or mRNA levels are associated with a cancer phenotype." Applicants do not agree.

Preliminarily, as acknowledged by the Office, the post-filing date reference correlates calcineurin levels with colon cancer. The Office has failed to point out what experimentation would be necessary, less still what experimentation would be undue, in order to diagnose other cancers presently claimed, e.g. carcinoma, lymphoma, prostate cancer, stomach cancer and breast cancer. Additionally, the Office has provided no factual evidence teaching or reasonably suggesting that production of PPP3CC protein in the colon is not coordinately regulated with transcription of the gene encoding the protein. See *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971) ("[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.")

Further, it appears that the Office may be requiring as proof of enablement information and data outside the scope of the enablement requirement. For example, the Office cites several references discussing, *inter alia*, considerations necessary in bringing a cancer biomarker to successful ***clinical*** application. The Office alleged that "the application of a marker for diagnostic purposes requires a provision of a clear definition of the end point for which the candidate protein or gene is to be a marker; an identification of the relevant clinical specimen in which to detect the marker, and the establishment of a range of marker variability."

The fact that one of ordinary skill in the art would perhaps need to perform, for FDA approval purposes, additional validation studies of a prospective biomarker, and the fact that such studies might be considerable, are largely irrelevant and also not sufficient to support the Office's contention that the claims are not enabled. Applicants respectfully point out that questions regarding diagnostic marker efficacy and validation, for example, are more properly left for agencies other than the Patent and Trademark Office. As set forth in the "Training Materials For Examining Patent Applications With Respect To 35 U.S.C. Section 112, First Paragraph - Enablement Of Chemical/Biotechnical Application," considerations made by the FDA for approving clinical trials and drug products are different from those made by the PTO in

determining whether a claim is enabled. Clearly, validating biomarkers with respect to human clinical diagnostic efficacy is a task more properly within the purview of the FDA rather than the PTO.[1]

If the Examiner is looking for evidence of drug safety or human testing as required for FDA approval, it is clear that this is more than the statute requires. The courts have long held that this is not a proper level of inquiry when determining utility and enablement under Title 35. For example, in *In re Watson*, 517 F.2d 465, 476 (C.C.P.A. 1975), the court stated "Congress has given the responsibility to the FDA, not to the Patent Office, to determine in the first instance whether drugs are sufficiently safe for use ...." The U.S. Court of Appeals for the Federal Circuit has followed this lead, and made clear in *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994), that "[t]esting for the full safety and effectiveness of a [claimed invention] is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings. It is clear that one can enable a claim of treating cancer without having FDA approval or having performed clinical trials.

Additionally, although Applicants maintain that the requirements set forth in Tockman are not requirements of the patent laws, Applicants point out that the present application provides at least two of the three alleged "Tockman" requirements. The present application sets forth the endpoint for which the candidate protein or gene is to be a marker for (colon cancer, leukemia, carcinoma, lymphoma, prostate cancer, stomach cancer and breast cancer) as well as expression levels indicative of the cancer. The present application further provides an indication of the

---

[1] *See also In re Brana*: "The Commissioner counters that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means *in vivo* testing in humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans. The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. *See Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.")."

relevant clinical specimen (colon tissue, lymphatic tissue, prostate tissue, stomach tissue and breast tissue.).

The Office further rejects claims 20-27 and 29-35 under 35 U.S.C. §112, first paragraph (enablement), alleging that the specification does not enable the full scope of the broadest claim, asserting that the broadest claim "may be interpreted as a method for diagnosis of cancer comprising detecting evidence of differential expression of a sequence having greater than 75% overall homology to SEQ ID NO:1587." Applicants do not agree. As discussed, above, the claims have been amended to refer to specific cancers. Further the claims were revised to note that the expression products are at least 98% identical to SEQ ID NO:1587. Although the specification does disclose that "CA nucleic acids" can have at least 75% overall homology to one of the nucleic acids set forth in Tables 1-112, the pending claims limit this scope of homology to at least 98% identity. Applicants respectfully assert that the full scope of the pending claims is enabled.

In conclusion, the specification enables one of ordinary skill in the art to make and use the claimed invention. Accordingly, Applicants respectfully request that the rejection of claims 20-35 under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

Rejections under 35 U. S. C. § 102

Claims 20-24 were rejected under 35 U.S.C. 102(e) as allegedly anticipated by U.S. Patent number 6,812,339 (hereinafter the "Venter patent"). The Office alleges that the Venter patent discloses a sequence (SEQ ID NO:771)that "is the same as applicants' SEQ ID NO:1587) and that "Venter's method comprises the same active step as recited in claims 20-24". (Office Action pages 12-13). Because the Venter patent fails to disclose each and every limitation of claims the pending claims, Applicants respectfully disagree.

Preliminarily, Applicants note that claim 20 was amended. As amended, claim 20 requires determining whether there is an increase in the level of the PP3CC expression product of at least 50% compared to a non-cancerous control. Claims 21-24 were cancelled without prejudice.

The Venter patent is entitled "Polymorphisms In Known Genes Associated With Human Disease, Methods Of Detection And Uses Thereof" and is:

> based on the discovery of novel polymorphisms (SNPs) in the genes known in the art ... The present invention provides reagents used for detecting and expressing the variant nucleic acid/protein sequence as well as methods of identifying and using these variants.

Although the Venter patent discusses close to 6000 genes (SEQ ID NOS:11743-17613) as well as the transcripts (SEQ ID NOS:1-5871) and encoded protein sequences (SEQ ID NOS:5892-11742) of these genes, Venter fails to teach or even suggest the present invention.

With respect to claim 20 as amended, the Office has failed to provide any reference in Venter to an increase of at least 50% in the level of a PPP3CC expression product as indicative of any cancer, less still of colon cancer. Venter further fails to teach that an increase of at least 50% in PPP3CC gene product is indicative of carcinoma, lymphoma, prostate cancer, stomach cancer and breast cancer. Accordingly, Venter does not anticipate or even suggest the presently claimed invention.

Claims 20-26, 29, 30 and 34 were rejected under 35 U.S.C. 102(b) as allegedly anticipated by Yamamoto *et al.* (Leukemia (1999) 13:595-600; hereinafter the "Yamamoto reference"). The Office alleges that Yamamoto discloses a "method of measuring the level of PP2B protein (calcinueirn; a protein that is encoded by SEQ ID NO:1587, which encodes PPP3CC) in leukemic cells from patients with acute myelogenous leukemia (AML), common acute lymphocytic leukemia (cALL), and chronic lymphocytic leukemia (CLL) and in normal peripheral leukocytes (page 596, 1st to 2nd column, bridging paragraph; and 2nd column). Although Applicants respectfully disagree because, *inter alia*, Yamamoto fails to teach SEQ ID NO:1587, much less comparing expression levels of SEQ ID NO:1587 (Applicants note that SEQ ID NO: 1587 is 99% identical to the catalytic subunit, gamma isoform (PPP3CC) (NM_005605.3), solely in an attempt to advance the prosecution of the pending claims to allowance, the claims have been revised. As revised, the claims no longer read on methods of diagnosing leukemia.

In view of the foregoing, Applicants respectfully request the withdrawal of the rejections under 35 U.S.C. § 102.

CONCLUSION

The foregoing represents a bona fide attempt to advance the present application to allowance. Applicants respectfully assert that all claims are in condition for allowance, which action is hereby requested. The Examiner is invited to telephone the undersigned attorney at (302) 778-8458 if such would expedite prosecution.

No fee is believed due. Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: May 11, 2007

Gwilym J. O. Attwell
Reg. No. 45,449

Fish & Richardson P.C.
P.O. Box 1022
Minneapolis, MN 55440-1022
Telephone: (302) 652-5070
Facsimile: (877) 769-7945